facing a true epidemic of glomerular sclerosis, dissecting its pathogenesis, one pathway at a time, is a welcome step. We cannot devise effective therapies for glomerular sclerosis unless we know its pathomechanism. We need to identify and learn how to control the responsible receptors triggering the pathways to sclerosis.

DISCLOSURE
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Vitamin D supplementation after renal transplantation: how much vitamin D should we prescribe?

Ronen Levi[1] and Justin Silver[1]

Vitamin D deficiency is common in patients with chronic kidney disease after renal transplantation. Vitamin D, essential for mineral and bone metabolism, also has myriad beneficial autocrine effects on intact immune responses and defense against infection, as well as suppression of malignant changes. Supplementation with oral parental vitamin D could correct this problem. Courbebaisse *et al.* define how much oral vitamin D to prescribe to renal allograft recipients.

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Vitamin D is an ancient hormone identified in the ocean-drifting organisms, the plankton that evolved over 750 million years ago. Without plankton there would be no life, and phytoplankton have the essential capacity not only to recycle carbon but also to synthesize vitamin D. The ingestion of plankton in the depths of the oceans provides the vitamin D content of fish, and hence a plentiful supply for fish-eating humans. In the cauldrons of time *Homo sapiens* evolved half a billion years later, developed remarkable cognitive neurodevelopment, and retained the ability to efficiently synthesize vitamin D_3 or cholecalciferol when exposed to the ultraviolet B rays of sunlight. However, we are constrained by a limited opportunity to bare our bodies to the joys of the sun, clouded by a concern for the harmful effects of excess ultraviolet B rays. Transplant patients are well advised to limit their exposure to the ultraviolet B rays and their potentially damaging effects because a well-documented complication of immunosuppressive therapy is the far greater incidence of skin cancers.[1] But what about the beneficial effects of ultraviolet B in initiating the photosynthesis of cholecalciferol in their keratinocytes? Vitamin D is critically important for the development, growth, and maintenance of a healthy skeleton from birth until death. The major function of vitamin D is to maintain calcium homeostasis. It accomplishes this by increasing the efficiency with which the intestine absorbs dietary calcium. When there is inadequate calcium in the diet to satisfy the body's calcium requirement, vitamin D and other humoral and local factors communicate to the osteoblasts that then signal osteoclast precursors to mature and dissolve the calcium stored in the bone.[2] Vitamin D_3 is metabolized in the liver to produce 25-hydroxyvitamin D_3 (25(OH)D) and then in the kidney to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D$), the biologically active form of the vitamin. $1,25(OH)_2D$ acts on its receptors, the vitamin D receptors, which are present not only in the intestine and bone, but in a wide variety of other tissues, including the brain, heart, stomach, pancreas, activated T and B lymphocytes, skin, and gonads. Muscle function, innate immunity, cellular growth and maturation, immunomodulation, and insulin secretion, as well as the regulation of calcium, phosphorus, and bone metabolism, are all affected or controlled by vitamin D (Figure 1). $1,25(OH)_2D$ is one of the most potent substances to inhibit proliferation of both normal and hyperproliferative cells and induce them to mature. It is also recognized that apart from the $1,25(OH)_2D$ synthesized and

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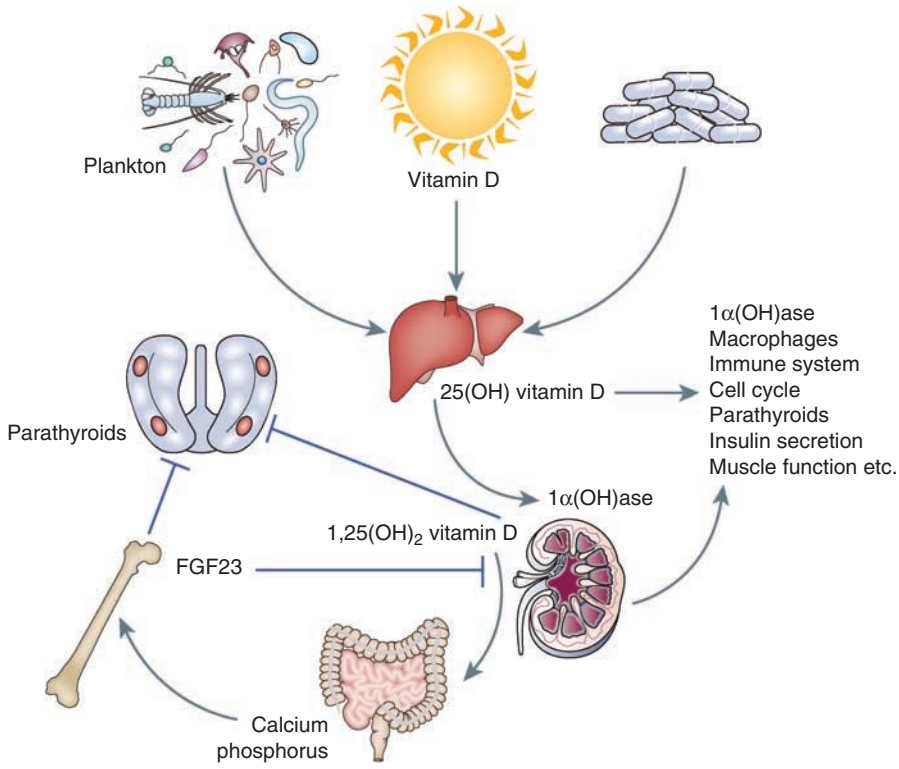

Figure 1 | Metabolic, endocrine, and autocrine action of vitamin D. FGF23, fibroblast growth factor-23.

secreted by the kidney, a wide variety of tissues, including parathyroid, colon, prostate, breast, and skin, have the enzymatic machinery to produce $1,25(OH)_2D$, which then has a local autocrine or paracrine action rather than a systemic hormonal action.[2]

The regulation of mineral metabolism in physiology and disease has taken great strides recently with the elucidation of the sequences of events in the development of the changes in mineral and bone disease in chronic kidney disease (CKD). Specifically, it is now apparent that fibroblast growth factor-23 (FGF23), secreted by osteocytes, is increased in CKD, in part by the stimulus of the phosphate retention of CKD.[3] The increased levels of FGF23 then act on its receptor, Klotho-FGFR1c, in the kidney and the parathyroid.[4,5] In the kidney, it decreases the synthesis of $1,25(OH)_2D$ and leads to phosphaturia, and in the parathyroid, it decreases parathyroid hormone (PTH) gene expression and PTH secretion.[5] Despite the decreased serum $1,25(OH)_2D$ levels in patients with CKD, due to a direct inhibitory effect of a raised serum phosphate as well as FGF23 action, we should not be satisfied with just prescribing $1,25(OH)_2D$ or its analogues. We must also ensure that our patients have adequate levels of 25(OH)D, which reflects their nutritional vitamin D status and provides a substrate for the local synthesis of $1,25(OH)_2D$, which may then exert its myriad local autocrine effects, which are all beneficial to health. Vitamin D deficiency is a major unrecognized health problem. Not only does it cause rickets in children, and osteomalacia in adults, but it may have long-lasting effects on other organ systems.

Epidemiological evidence has been accruing for the past 40 years that low vitamin D levels are associated with a large number of diverse diseases. These include cancer of the breast, prostate, and colon as well as diabetes mellitus and tuberculosis.[2] Recent experimental studies have been astoundingly refreshing and insightful in shedding light on the mechanisms involved. There is thus every reason to ensure that the patients we treat and all our fellow citizens are in a vitamin D-replete state. It has been difficult to define vitamin D repletion.[6] To wait for the consequences of a low serum calcium leading to secondary hyperparathyroidism with correction of the serum calcium at the expense of bone and the trade-off of phosphaturia is to miss the boat and expose people unnecessarily to the complications of vitamin D insufficiency. We now have target levels of 25(OH)D, which we should aspire to reach, but even these levels may be set too low. You will be surprised how many around you, including yourselves, family, and colleagues, do not reach these levels. They are serum 25(OH)D of greater than 30 ng/ml. Less than 30 ng/ml but greater than 15 ng/ml is vitamin D insufficiency and exposure to all the ills of too little vitamin D. Less than 15 ng/ml is vitamin D deficiency, which is dangerous. Patients with CKD have long been known to suffer from vitamin D deficiency, which is an integral component in the pathogenesis of renal bone disease.[7] A recent analysis of data from the Third National Health and Nutrition Examination Survey showed that in a large sample of more than 15,000 study participants, 25(OH)D levels less than 30 ng/ml are much more prevalent in CKD patients than in the general population, affecting nearly a third of the participants, and this was not related to differences in dietary intake.[8] How much vitamin D to prescribe? Well, we really have been pretty much in the dark. So the article by Courbebaisse *et al.*[9] in this issue of *Kidney International*[9] is particularly welcome.

Courbebaisse *et al.*[9] compared outcomes in patients with 25(OH)D concentration less than 30 ng/ml and normal serum calcium, treated or not treated with cholecalciferol. They showed that treating patients with 100,000 units of cholecalciferol every 2 weeks for 2 months may be enough to significantly elevate serum levels of 25(OH)D to above 30 ng/ml and reduce PTH levels without consequent hypercalcemia or increased urinary calcium excretion, which could adversely affect graft function. However, during the less intensive phase of the treatment, when cholecalciferol was given at the same dose every other month, serum levels of 25(OH)D decreased again, though they remained higher than in control untreated patients at 1 year after transplantation. The message to be drawn from this study is that we need to prescribe large doses of cholecalciferol for our patients after renal transplantation. In addition, we need similar bold studies on the correct dose of cholecalciferol or ergocalciferol to prescribe for our patients at the different stages of CKD.[10]

Current Kidney Disease Outcomes Quality Initiative guidelines define deficiency of vitamin D metabolites as less than 15 ng/ml for $25(OH)D_3$, but this does not account for the other consequences of vitamin D insufficiency. The first parameter of mineral metabolism to be decreased in patients with early CKD was shown by Levin *et al.*[11] to be serum $1,25(OH)_2D$. That is an important observation, and it would be of great interest to test the response of those patients with early CKD to oral vitamin D rather than oral $1,25(OH)_2D$ or its analogues.

Until then, it is incumbent upon us to increase the dose and maintain levels of 25(OH)D in all our patients and in the general population where we may have some small influence. We need to rise to the challenge and make broad public appeals for wider supplementation with vitamin D and a prudent exposure to sunlight.

DISCLOSURE
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Creatinine and cystatin C: what are the values?

Linda F. Fried[1,2,3]

Recent studies indicate that serum cystatin C is a better marker of glomerular filtration rate (GFR) and is a stronger predictor of cardiovascular disease and mortality than serum creatinine. Before cystatin C can gain wide acceptance, information about factors that affect generation, elimination, and analysis is needed. Stevens *et al.* analyze non-GFR–related factors associated with cystatin C and creatinine levels. The results will be useful in interpreting cystatin C levels in research and clinical practice.

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Measuring glomerular filtration rate (GFR) in every patient is not practical in clinical care or large epidemiologic studies. This leaves us with estimation of GFR using endogenous markers, such as creatinine and cystatin C. The ideal endogenous marker does not exist. An ideal marker would have a constant generation rate, be freely filtered at the glomerulus, have no tubular secretion or reabsorption, and have no extrarenal clearance. In order to interpret levels of any proposed marker used in estimation of GFR, it is important to understand the factors that alter the generation, elimination, and analysis. The factors associated with creatinine are well understood, but this is not the case with cystatin C. Cystatin C is a 120-amino acid cysteine protease inhibitor. It is produced and secreted by all nuclear cells.[1] It functions extracellularly to inhibit papain-like cysteine protease inhibitors.[2] It is freely filtered at the glomerulus, reabsorbed by proximal tubules via megalin-mediated endocytosis, and catabolized.[3]

Stevens *et al.*[4] (this issue) analyzed the associations with cystatin C and

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